Sphingosine 1-Phosphate Metabolism and Signaling

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Abstract

Sphingosine 1-phosphate (S1P) is a well-defined bioactive lipid molecule derived from membrane sphingolipid metabolism. In the past decades, a series of key enzymes involved in generation of S1P have been identified and characterized in detail, as well as enzymes degrading S1P. S1P requires transporter to cross the plasma membrane and carrier to deliver to its cognate receptors and therefore transduces signaling in autocrine, paracrine, or endocrine fashions. The essential roles in regulation of development, metabolism, inflammation, and many other aspects of life are mainly executed when S1P binds to receptors provoking the downstream signaling cascades in distinct cells. This chapter will review the synthesis, degradation, transportation, and signaling of S1P and try to provide a comprehensive view of the biology of S1P, evoking new enthusiasms and ideas into the field of the fascinating S1P.

Keywords

Sphingosine 1-phosphate · Sphingolipid metabolism · Receptor signaling

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6.1 Synthesis of S1P

The synthesis of S1P is illustrated in Fig. 6.1. Although it has been documented that the synthesis of S1P could occur intra- and extracellularly [1], recent reports favor the notion that intracellular synthesis is the major contribution of S1P production under physiological condition [2]. The instant reaction to produce S1P from sphingosine involves two characterized kinases, namely sphingosine kinase (SK or SphK) 1 and SK2 [3–6].

6.2 S1P Kinases

Although two human genes encoding SK1 and SK2 are located on different chromosomes with *SK1* on the chromosome 17 and *SK2* on the chromosome 19, they are evolutionarily conserved lipid kinases with five highly conserved motifs (named C1–5) [7, 8]. Among them, a C4 motif is considered as unique to the SKs superfamily [8] and confines substrate recognition [9]. Analysis of crystal structure of SK1 determined a two-domain architecture model with the C-terminal domain accommodating a substrate-binding pocket formed by C4 and C5 motifs [10], providing a prototype for understanding the molecular basis of the catalytic sites and substrate specificity of SKs. Both SK1 and SK2 phosphorylate dihydro- and sphigosine, although phosphorylation catalyzed by SK1 is much more

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efficient than by SK2 [11]. SK2 has broader substrate spectrum, including phytosphingosine [6] and the spingoid base analog FTY720 or its derivative [12–15].

Bulk majority of SK1 is present in the cytosol; however, a small portion of SK1 is translocated to the plasma membrane, cytoskeleton, and intracellular organelles, such as endoplasmic reticulum (ER) and phagosome upon stimulation [16–18]. The compartmentalization and translocation of SK1 not only make it closer to its substrate, sphingosine, which is embedded in the lipid bilayer, but encounter with its regulators [8]. For example, extracellular signal-regulated kinase (ERK) 1/2-mediated phosphorylation of SK1 at Ser225 promotes conformational change of SK1, which leads to plasma membrane translocation and an increase of catalytic activity [19]. Moreover, interacting with the calcium- and integrin-binding protein 1 is required for induction of membrane translocation of SK1 in a calcium-dependent manner [20]. In contrast, SK2 was found shuttling between the cytoplasm and the nucleus [19]. SK2 has 234 more amino acids (AAs) than that of SK1 (384 AAs), in which additional nuclear localization and exportation signal motifs are located [21, 22]. The S1P generated in the nucleus was reported to involve in epigenetic regulation of gene transcription [23]. SK2 is also found in intracellular organelles, including mitochondria [24] and ER [25]. Interestingly, apoptotic cells release SK2, which in return increases local S1P concentration in regulation of immune responses [26]. These in vitro studies indicate that SK1 and SK2 may regulate different pools of S1P despite many shared properties.

Indeed, studies from knockout (KO) mouse models showed that Sk1 and Sk2 contributed differently to tissue and serum levels of S1P, but share some redundant functions, which allowed them to compensate each other for the single KO mice to survive since none of the double KO mice survived beyond embryonic day 13.5 due to intracranial bleeding [27, 28]. The single KO mice have normal or slightly reduced S1P levels in most tissues, while the serum S1P in Sk1-KO mice was reduced by 50% while the Sk2-KO mice has an increased serum S1P level [29, 30]. However, the lymphocyte cellularity and distribution in the lymphatic organs, which is controlled by S1P, was not affected in the Sk1-KO mice, indicating that reduced serum pool of S1P was sufficient for the lymphocyte trafficking [27]. Further studies found that Sk1-KO mice exhibited normal immune responses in mouse model of thioglycollate-induced peritonitis or collage-induced arthritis [31]. In other words, the S1P gradient (will discuss in detail below) regulating lymphocyte traffic was not disrupted by Sk1 deletion. Instead, the reduced serum S1P level by Sk1 deletion resulted in more severe neuroinflammation in a LPS-induced brain injury model [32], whereas the increased serum S1P by Sk2 deficiency reduced atherosclerotic lesions in a mouse model of atherosclerosis [30], suggesting the serum level of S1P is rather likely affecting vascuar functions via endothelail $S1P_1$ [33].

6.3 S1P Degradation

S1P level is determined by the balance of synthesis and degradation (Fig. 6.1). As discussed above, the synthesis of S1P is mainly catalyzed by two specific kinases; the degradation of S1P also requires several designated enzymes. On the one hand, S1P is dephosphorylated to sphingosine by three lipid phosphate phosphatases (LPPs, encoded by *Lgpps* in mouse genome) and two S1P-specific phosphatases (SPPs, encoded by *Sgpps* in mouse genome) identified up to date [34]. On the other hand, S1P is irreversibly hydrolyzed by the S1P lyase (SPL, encoded by *Sgpl1* in mouse genome) [35].

6.4 S1P Phosphatases

Both SPPs and LPPs belong to the type 2 lipid phosphate phosphohydrolases family with three conserved domains at the predicted enzyme active site, despite LPPs have broader substrate specificity than that of SPPs [34, 36]. LPPs are located on the plasma membrane with its active site on the outer leaflet and thus dephosphorylate

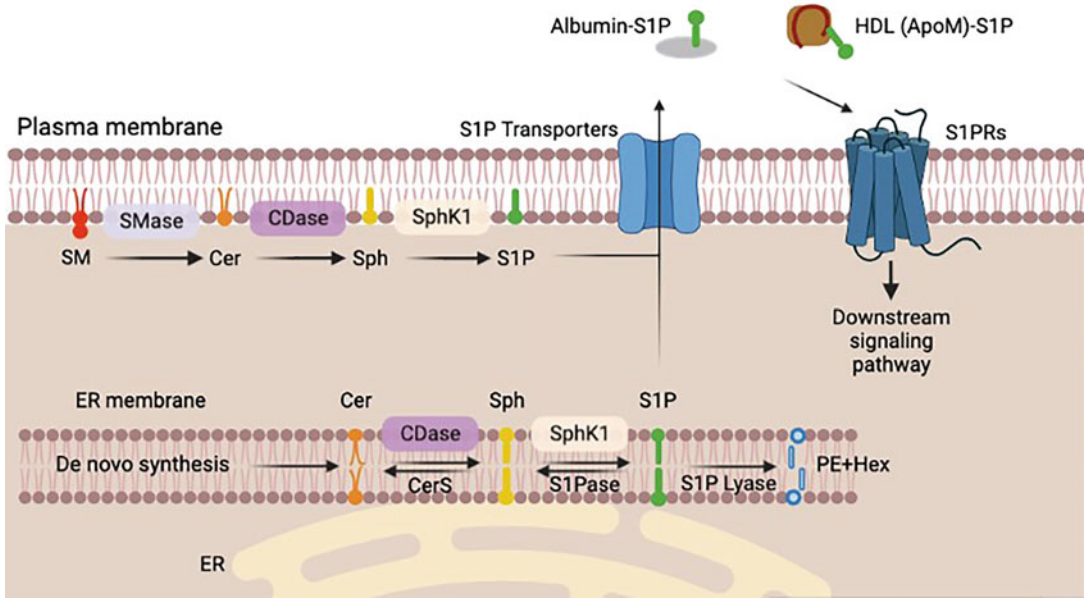

Fig. 6.1 Schematic presentation of intracellular metabolism of sphingolipid and extracellular transportation of S1P. In the ER, ceramide (Cer) generated from the de novo synthesis pathway is hydrolyzed by ceramidase (CDase) to yield sphingosine (Sph) which in return is phosphorylated by Sph kinase 1 (SphK1) to produce S1P. S1P is constantly dephosphorylated by S1P phosphatase (S1Pase) to recycle Sph back to synthesis of sphingolipid. Conversely, S1P is degraded by S1P lyase to yield phosphoethanolamine (PE) and hexadecenal (Hex). The two end products of S1P breakdown are consumed by a salvage pathway to enter the cycle of phospholipid metabolism. In the plasma membrane, sphingomyelin (SM) is catalyzed by sphingomyelinase (SMase) and subsequentially CDase to yield Sph for SphK1 to generate S1P. The intracellular synthesized S1P is actively transported across the plasma membrane by designated S1P transporters and transfer onto carriers to produce albumin-S1P and ApoM-S1P for signaling transduction when they bind to S1P receptors (S1PRs)

the extracellular pool of S1P [36]. Other substrates of LPPs include lysophosphatidic acid (LPA), phosphatidate, ceramide 1-P, and FTY720-P. And mouse genetic studies suggest that LPA is likely the favorable substrate of LPPs [36]. In contrast, SPPs are more substrate-specific phosphatases that dephosphorylate S1P, dihydro-S1P, and phyto-S1P, mediating the recycling of sphingoid bases into different metabolic pathways [37–39]. Mammalian SPPs locate in the ER and consist of two isoforms, SPP1 and SPP2 [34]. SPP1 regulates the intra- and extracellular levels of S1P and is essential for cell viability in vitro [40]. Gene-deletion studies revealed that *Sgpp1*-KO mice developed an ichthyosis-like phenotype a few days after birth; *Sgpp1*-KO keratinocytes had increased intracellular level of S1P and accelerated cellular differentiation [41]. *Sgpp2*-KO mice exhibited normal pancreatic islet size but defective β-cell proliferation when challenged with either high-fat diet or a specific β-cell toxin; mechanistic studies showed that SPP2 plays pivotal role in ER stress and proliferation of the β-cell [42]. These findings indicate that LPPs and SPPs are dispensable for the S1P levels in tissues or the circulation.

6.5 S1P Lyase

Unlike LPPs and SPPs that recycle sphingosine, SPL cleaves S1P to yield ethanolamine phosphate and hexadecanol taking the sphingoid base out of recycling [43]. SPL is a single-pass ER membrane protein exerting its enzymatic activity in homodimers [44] and is highly expressed in

tissues with rapid cell turnover, including small intestines, colon, thymus, and spleen [45]. High level of SPL expression is associated with low level of S1P in the tissues whereas its absence in the red blood cells (RBCs) and platelets maintains high S1P level in the plasma. Therefore, SPL is the key enzyme guarding the chemotactic S1P gradient between tissue and blood, enabling egress of lymphocytes [46].

The pivotal role of SPL in regulation of development, metabolism, and inflammation has been illustrated in *Sgpl1*-KO mouse models [47]. Besides lymphopenia, the *Sgpl1*-KO mice were reported to manifest developmental retardation, thymic atrophy, neutrophilia, hyperostosis, and nephrosis [48–52]. Lack of SPL leads to intra- and extracellular accumulation of S1P which has toxic effects [53], as well as dysregulation of global lipid metabolism, such as increased ceramides, sphingomyelins, phospholipids, triacyglycerols, diacylglycerols, and cholesterol esters [52]. In a mouse model of chemically induced colitis, the intestinal epithelial cell-specific deletion of *Sgpl1* led to more severe disease conditions and promoted colon carcinogenesis [54]. Gene polymorphisms associated with *SGPL* have been shown to be related to the susceptibility of late-onset Alzheimer's disease [55]. Recent discoveries about a new inborn error of sphingolipid metabolism caused by loss-of-function mutations of *SGPL* closely translated the previous findings obtained from cultured cells and mouse models, indicating that SPL is essential for sphingolipid homeostasis.

6.6 Transportation of S1P and Transporters

S1P contains a hydrophilic head group and a hydrophobic tail, which renders itself water incompatible. S1P requires designated binding partners, like transporters and carriers (Fig. 6.1), to move around along the circulation.

As a lysophospholipid molecule, intracellular S1P requires transporters to export across the cytoplasmic membrane. Initially, in vitro studies suggested that some of the ATP-binding cassette transporter family members were candidates as S1P transporters and might be responsible for exporting S1P to plasma. However, results of S1P measurement in plasma from gene-deletion mouse model ruled out this possibility (reviewed by Hla et al. [56]). The protein spinster homolog 2 (Spns2) is the first identified mammalian S1P-specific transporter [57–60]. Spns2 is enriched in vascular and lymphatic endothelial cells (LECs), regulating S1P concentration mainly in the lymph [60]. Spns2 in LECs is essential to maintain S1P gradient between lymphatic tissue and lymph and governs lymphocyte migration and survival [60–62], suggesting Spns2 is functioning on the apical membrane of LECs. A recent study, interestingly, provided evidence that Spns2 partners with the major facilitator superfamily domain-containing protein 2a (Mfsd2a) to release S1P into basolateral space of mouse brain ECs and to preserve the blood brain barrier function [63]. Mechanism underlying membrane localization of Spns2 in different ECs merits further investigation. Mfsd2b is the second definitively verified S1P transporter which is required for exporting S1P out of RBCs, sustaining static plasma S1P concentration [64]. Under thrombosis condition, Mfsd2b is required for the activated platelets to release S1P [65]. Mouse genetic studies on Mfsd2b and Spns2 have fortified the notion that RBC-S1P is the most important source for the plasma S1P, whereas the LEC-S1P is the major contributor of the lymphatic S1P. Therefore, targeting specific S1P transporters might be a promising therapeutic strategy to differentially inhibit S1P signaling on different cell types [65, 66].

Both transporters are multi-pass transmembrane proteins and mainly expressed on the cell surface [64, 67, 68]. Two recent reporters on 3D structure of Mfsd2a orthologs revealed the tropisms and critical amino acids of the lysolipid-binding cavity of MFD family proteins [69, 70], providing analogous blueprint for the substrate-binding cavity of Spns2 and Mfsd2b. Based on the resolved crystal structure of Mfsd2a [70] and computational predictions by AlphaFold [71], one may postulate that the

S1P-binding pockets of Spns2 and Mfsd2b are composed of 12 transmembrane helices divided into two pseudo-symmetric six-helices bundles. Several pocket-lining amino acids of human MFSD2B derived from homologous analysis with MFSD2A are embedded in the transmembrane helixes and critical for substrate export [69, 70], suggesting that S1P gains access into the binding pocket is likely from within the membrane bilayer [64]. However, further investigation is obligated to justify the amino acids which define the S1P-binding specificity.

6.7 S1P Carriers

As an amphipathic lipid in nature, there is no free S1P in the aqueous phase. It has been estimated that ~54% of plasma S1P is associated with HDL, ~35% is bound to albumin, and the rest might associate with other lipoproteins [72, 73]. The HDL-associated apolipoprotein M (apoM) is the solo high affinity S1P-binidng protein identified to date with a well-defined binding pocket inside [74]. ApoM increased not only S1P in the plasma by increasing its solubility and protecting it from degradation, but also modulate the homeostasis of plasma S1P levels [74, 75]. ApoM regulates S1P function by facilitating its interaction with its receptors, thus enhances its biological functions in maintaining endothelial barrier and limiting endothelial inflammation [33, 76, 77]. Recently, an engineered S1P chaperone apoM-Fc was reported to efficiently activate S1P receptors in vitro and in vivo, providing potential therapeutic strategy for hypertension and ischemia-reperfusion injury of vital organs [78]. However, how and when S1P gets into apoM remain mysterious.

In contrast to the specific binding of apoM and S1P, albumin-associated S1P can be more considered as its free form [79]. The presence of albumin may only increase the solubility of S1P instead of actual physical binding. Further studies showed that albumin-associated S1P plays a controversial role in the pathogenesis of atherosclerosis, comparing with the protective role of apoM/HDL-associated S1P [80]. Nevertheless, fair amount of serum S1P is still present in the double KO of *apoM* and *albumin* mice [73] rendered further investigation for precise regulation of serum-S1P.

6.8 S1P Signaling Receptors

The extracellular S1P evokes intracellular signaling transduction via its five high affinity cognate receptors, named as $S1P_1$-$S1P_5$ [81]. And these receptors belong to the class A G-protein coupled receptor (GPCR) family [82]. The cell-type specific and dynamic expression of these five receptors differs vastly in various stages of life. Numerous publications have reported very broad expression and functionalities of $S1P_1$, $S1P_2$, and $S1P_3$ [83]. The confirmed cell types include, but not limited to, endothelial cells (ECs), immune cells, neural cells, myocytes, and fibroblasts. Interestingly, the same receptor residing on different cell types exerts opposite or similar regulatory consequences, while different receptors expressed on the same cell type may act opposingly or coordinatingly [83]. For instance, activation of $S1P_1$ in EC and macrophage is anti-inflammatory, whereas activation of astrocyte-$S1P_1$ increases release of pro-inflammatory cytokines; $S1P_1$ promotes vascular barrier function, while $S1P_2$ and $S1P_3$ damage the barrier in ECs; $S1P_2$ and $S1P_3$ function cooperatively to induce fibrosis in various tissues [84–87]. Recent studies using $S1P_1$ reporter mouse models presented exciting observations of spatial-temporal activation of $S1P_1$ related to endothelial transcriptional regulation [88] and immune cell maturation [89], which opens a new avenue for studying the heterogeneity of S1P/$S1P_1$ signaling.

$S1P_1$ is one of the most abundant and studied GPCRs. Many earlier effects have been focused on the binding partners (CD44, CD69, and β-arrestin), downstream signaling effectors ($G\alpha_i$, ERK, PI3K, Akt, phospholipase C, and Rac), and enzymatic modifiers of the intracellular domains of $S1P_1$ (Akt, GPCR kinase 2, and DHHC5). With more advanced genetic and proteomic screening technologies, LPA receptor 1 [90] and endoglin [91] were recently identified as the

crosstalk receptors of S1P/$S1P_1$ signaling. The former is also a GPCR acting upstream of $S1P_1$ to suppress S1P/$S1P_1$ signaling in lymphatic ECs [90]. The latter is an auxiliary receptor of TGF-β superfamily members acting downstream of $S1P_1$ to regulate EC barrier function and angiogenesis [92]. Although the crystal structure of $S1P_1$ was resolved together with a fusion protein tag and an antagonist, it at least provided a prototype for understanding how S1P gains access to its receptors and the substrate-binding pocket [93]. The authors suggested that S1P might slide into the amphipathic pocket, lined with charged and polar amino acid residues for the head of phospho-sphingolipid, from within the membrane bilayer. However, how the exogenous S1P maneuvers its way into the pocket demands more experimental innovations and logical inductions.

In contrast, expression of $S1P_4$ and $S1P_5$ is restricted to certain cell types, for instance, $S1P_4$ in myeloid cells, including T cell, B cell, macrophage or monocyte, neutrophil, eosinophil, mast cell, and dendritic cell [81, 83]. Functions of $S1P_4$ have been implicated in regulation of cell trafficking and differentiation [51, 94]. Expression of $S1P_5$ is limited to NKT cell [95] and oligodendrocyte [96, 97] though its mRNA was found in other myeloid cell types. However, the proposed function of $S1P_5$ has encountered contradictory findings [83]. Further experiments are required to sort out the role of $S1P_5$ signaling.

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References

1. Blaho, V. A., & Hla, T. (2011). Regulation of mammalian physiology, development, and disease by the sphingosine 1-phosphate and lysophosphatidic acid receptors. *Chemical Reviews, 111*, 6299–6320.
2. Engelbrecht, E., MacRae, C. A., & Hla, T. (2021). Lysolipids in vascular development, biology, and disease. *Arteriosclerosis, Thrombosis, and Vascular Biology, 41*, 564–584.
3. Melendez, A. J., Carlos-Dias, E., Gosink, M., Allen, J. M., & Takacs, L. (2000). Human sphingosine kinase: Molecular cloning, functional characterization and tissue distribution. *Gene, 251*, 19–26.
4. Nava, V. E., Lacana, E., Poulton, S., Liu, H., Sugiura, M., Kono, K., Milstien, S., Kohama, T., & Spiegel, S. (2000). Functional characterization of human sphingosine kinase-1. *FEBS Letters, 473*, 81–84.
5. Pitson, S. M., D'andrea, R. J., Vandeleur, L., Moretti, P. A., Xia, P., Gamble, J. R., Vadas, M. A., & Wattenberg, B. W. (2000). Human sphingosine kinase: Purification, molecular cloning and characterization of the native and recombinant enzymes. *The Biochemical Journal, 350*(Pt 2), 429–441.
6. Liu, H., Sugiura, M., Nava, V. E., Edsall, L. C., Kono, K., Poulton, S., Milstien, S., Kohama, T., & Spiegel, S. (2000). Molecular cloning and functional characterization of a novel mammalian sphingosine kinase type 2 isoform. *The Journal of Biological Chemistry, 275*, 19513–19520.
7. Kohama, T., Olivera, A., Edsall, L., Nagiec, M. M., Dickson, R., & Spiegel, S. (1998). Molecular cloning and functional characterization of murine sphingosine kinase. *The Journal of Biological Chemistry, 273*, 23722–23728.
8. Alemany, R., van Koppen, C. J., Danneberg, K., Ter Braak, M., Heringdorf, M. Z., & D. (2007). Regulation and functional roles of sphingosine kinases. *Naunyn-Schmiedeberg's Archives of Pharmacology, 374*, 413–428.
9. Yokota, S., Taniguchi, Y., Kihara, A., Mitsutake, S., & Igarashi, Y. (2004). Asp177 in C4 domain of mouse sphingosine kinase 1a is important for the sphingosine recognition. *FEBS Letters, 578*, 106–110.
10. Wang, Z., Min, X., Xiao, S. H., Johnstone, S., Romanow, W., Meininger, D., Xu, H., Liu, J., Dai, J., An, S., Thibault, S., & Walker, N. (2013). Molecular basis of sphingosine kinase 1 substrate recognition and catalysis. *Structure, 21*, 798–809.
11. Berdyshev, E. V., Gorshkova, I. A., Usatyuk, P., Zhao, Y., Saatian, B., Hubbard, W., & Natarajan, V. (2006). De novo biosynthesis of dihydrosphingosine-1-phosphate by sphingosine kinase 1 in mammalian cells. *Cellular Signalling, 18*, 1779–1792.
12. Kharel, Y., Lee, S., Snyder, A. H., Sheasley-O'neill, S. L., Morris, M. A., Setiady, Y., Zhu, R., Zigler, M. A., Burcin, T. L., Ley, K., Tung, K. S. K., Engelhard, V. H., Macdonald, T. L., Pearson-White, S., & Lynch, K. R. (2005). Sphingosine kinase 2 is required for modulation of lymphocyte traffic by FTY720. *The Journal of Biological Chemistry, 280*, 36865–36872.
13. Don, A. S., Martinez-Lamenca, C., Webb, W. R., Proia, R. L., Roberts, E., & Rosen, H. (2007). Essential requirement for sphingosine kinase 2 in a sphingolipid apoptosis pathway activated by FTY720 analogues. *The Journal of Biological Chemistry, 282*, 15833–15842.

14. Billich, A., Bornancin, F., Devay, P., Mechtcheriakova, D., Urtz, N., & Baumruker, T. (2003). Phosphorylation of the immunomodulatory drug FTY720 by sphingosine kinases. *The Journal of Biological Chemistry, 278*, 47408–47415.
15. Paugh, S. W., Payne, S. G., Barbour, S. E., Milstien, S., & Spiegel, S. (2003). The immunosuppressant FTY720 is phosphorylated by sphingosine kinase type 2. *FEBS Letters, 554*, 189–193.
16. Hengst, J. A., Guilford, J. M., Fox, T. E., Wang, X., Conroy, E. J., & Yun, J. K. (2009). Sphingosine kinase 1 localized to the plasma membrane lipid raft microdomain overcomes serum deprivation induced growth inhibition. *Archives of Biochemistry and Biophysics, 492*, 62–73.
17. Kusner, D. J., Thompson, C. R., Melrose, N. A., Pitson, S. M., Obeid, L. M., & Iyer, S. S. (2007). The localization and activity of sphingosine kinase 1 are coordinately regulated with actin cytoskeletal dynamics in macrophages. *The Journal of Biological Chemistry, 282*, 23147–23162.
18. Thompson, C. R., Iyer, S. S., Melrose, N., VanOosten, R., Johnson, K., Pitson, S. M., Obeid, L. M., & Kusner, D. J. (2005). Sphingosine kinase 1 (SK1) is recruited to nascent phagosomes in human macrophages: Inhibition of SK1 translocation by Mycobacterium tuberculosis. *Journal of Immunology, 174*, 3551–3561.
19. Pitson, S. M., Moretti, P. A., Zebol, J. R., Lynn, H. E., Xia, P., Vadas, M. A., & Wattenberg, B. W. (2003). Activation of sphingosine kinase 1 by ERK1/2-mediated phosphorylation. *The EMBO Journal, 22*, 5491–5500.
20. Jarman, K. E., Moretti, P. A., Zebol, J. R., & Pitson, S. M. (2010). Translocation of sphingosine kinase 1 to the plasma membrane is mediated by calcium- and integrin-binding protein 1. *The Journal of Biological Chemistry, 285*, 483–492.
21. Igarashi, N., Okada, T., Hayashi, S., Fujita, T., Jahangeer, S., & Nakamura, S. (2003). Sphingosine kinase 2 is a nuclear protein and inhibits DNA synthesis. *The Journal of Biological Chemistry, 278*, 46832–46839.
22. Ding, G., Sonoda, H., Yu, H., Kajimoto, T., Goparaju, S. K., Jahangeer, S., Okada, T., & Nakamura, S. I. (2007). Protein kinase D-mediated phosphorylation and nuclear export of sphingosine kinase 2. *The Journal of Biological Chemistry, 282*, 27493–27502.
23. Hait, N. C., Allegood, J., Maceyka, M., Strub, G. M., Harikumar, K. B., Singh, S. K., Luo, C., Marmorstein, R., Kordula, T., Milstien, S., & Spiegel, S. (2009). Regulation of histone acetylation in the nucleus by sphingosine-1-phosphate. *Science, 325*, 1254–1257.
24. Strub, G. M., Paillard, M., Liang, J., Gomez, L., Allegood, J. C., Hait, N. C., Maceyka, M., Price, M. M., Chen, Q., Simpson, D. C., Kordula, T., Milstien, S., Lesnefsky, E. J., & Spiegel, S. (2011). Sphingosine-1-phosphate produced by sphingosine kinase 2 in mitochondria interacts with prohibitin 2 to regulate complex IV assembly and respiration. *The FASEB Journal, 25*, 600–612.
25. Maceyka, M., Sankala, H., Hait, N. C., Le Stunff, H., Liu, H., Toman, R., Collier, C., Zhang, M., Satin, L. S., Merrill, A. H., Jr., Milstien, S., & Spiegel, S. (2005). SphK1 and SphK2, sphingosine kinase isoenzymes with opposing functions in sphingolipid metabolism. *The Journal of Biological Chemistry, 280*, 37118–37129.
26. Weigert, A., Cremer, S., Schmidt, M. V., von Knethen, A., Angioni, C., Geisslinger, G., & Brüne, B. (2010). Cleavage of sphingosine kinase 2 by caspase-1 provokes its release from apoptotic cells. *Blood, 115*, 3531–3540.
27. Allende, M. L., Sasaki, T., Kawai, H., Olivera, A., Mi, Y., van Echten-Deckert, G., Hajdu, R., Rosenbach, M., Keohane, C. A., Mandala, S., Spiegel, S., & Proia, R. L. (2004). Mice deficient in sphingosine kinase 1 are rendered lymphopenic by FTY720. *The Journal of Biological Chemistry, 279*, 52487–52492.
28. Mizugishi, K., Yamashita, T., Olivera, A., Miller, G. F., Spiegel, S., & Proia, R. L. (2005). Essential role for sphingosine kinases in neural and vascular development. *Molecular and Cellular Biology, 25*, 11113–11121.
29. Feuerborn, R., Besser, M., Poti, F., Burkhardt, R., Weissen-Plenz, G., Ceglarek, U., Simoni, M., Proia, R. L., Freise, H., & Nofer, J. R. (2018). Elevating endogenous sphingosine-1-phosphate (S1P) levels improves endothelial function and ameliorates atherosclerosis in low density lipoprotein receptor-deficient (LDL-R−/−) mice. *Thrombosis and Haemostasis, 118*, 1470–1480.
30. Zemann, B., Kinzel, B., Muller, M., Reuschel, R., Mechtcheriakova, D., Urtz, N., Bornancin, F., Baumruker, T., & Billich, A. (2006). Sphingosine kinase type 2 is essential for lymphopenia induced by the immunomodulatory drug FTY720. *Blood, 107*, 1454–1458.
31. Michaud, J., Kohno, M., Proia, R. L., & Hla, T. (2006). Normal acute and chronic inflammatory responses in sphingosine kinase 1 knockout mice. *FEBS Letters, 580*, 4607–4612.
32. Grin'kina, N. M., Karnabi, E. E., Damania, D., Wadgaonkar, S., Muslimov, I. A., & Wadgaonkar, R. (2012). Sphingosine kinase 1 deficiency exacerbates LPS-induced neuroinflammation. *PLoS One, 7*, e36475.
33. Galvani, S., Sanson, M., Blaho, V. A., Swendeman, S. L., Obinata, H., Conger, H., Dahlback, B., Kono, M., Proia, R. L., Smith, J. D., & Hla, T. (2015). HDL-bound sphingosine 1-phosphate acts as a biased agonist for the endothelial cell receptor S1P1 to limit vascular inflammation. *Science Signaling, 8*, ra79.
34. Pyne, S., Kong, K. C., & Darroch, P. I. (2004). Lysophosphatidic acid and sphingosine 1-phosphate biology: The role of lipid phosphate phosphatases. *Seminars in Cell & Developmental Biology, 15*, 491–501.

35. Zhou, J., & Saba, J. D. (1998). Identification of the first mammalian sphingosine phosphate lyase gene and its functional expression in yeast. *Biochemical and Biophysical Research Communications, 242*, 502–507.
36. Tang, X., Benesch, M. G., & Brindley, D. N. (2015). Lipid phosphate phosphatases and their roles in mammalian physiology and pathology. *Journal of Lipid Research, 56*, 2048–2060.
37. Giussani, P., Maceyka, M., Le Stunff, H., Mikami, A., Lepine, S., Wang, E., Kelly, S., Merrill, A. H., Jr., Milstien, S., & Spiegel, S. (2006). Sphingosine-1-phosphate phosphohydrolase regulates endoplasmic reticulum-to-golgi trafficking of ceramide. *Molecular and Cellular Biology, 26*, 5055–5069.
38. Le Stunff, H., Giussani, P., Maceyka, M., Lepine, S., Milstien, S., & Spiegel, S. (2007). Recycling of sphingosine is regulated by the concerted actions of sphingosine-1-phosphate phosphohydrolase 1 and sphingosine kinase 2. *The Journal of Biological Chemistry, 282*, 34372–34380.
39. Le Stunff, H., Galve-Roperh, I., Peterson, C., Milstien, S., & Spiegel, S. (2002). Sphingosine-1-phosphate phosphohydrolase in regulation of sphingolipid metabolism and apoptosis. *The Journal of Cell Biology, 158*, 1039–1049.
40. Johnson, K. R., Johnson, K. Y., Becker, K. P., Bielawski, J., Mao, C., & Obeid, L. M. (2003). Role of human sphingosine-1-phosphate phosphatase 1 in the regulation of intra- and extracellular sphingosine-1-phosphate levels and cell viability. *The Journal of Biological Chemistry, 278*, 34541–34547.
41. Allende, M. L., Sipe, L. M., Tuymetova, G., Wilson-Henjum, K. L., Chen, W., & Proia, R. L. (2013). Sphingosine-1-phosphate phosphatase 1 regulates keratinocyte differentiation and epidermal homeostasis. *The Journal of Biological Chemistry, 288*, 18381–18391.
42. Taguchi, Y., Allende, M. L., Mizukami, H., Cook, E. K., Gavrilova, O., Tuymetova, G., Clarke, B. A., Chen, W., Olivera, A., & Proia, R. L. (2016). Sphingosine-1-phosphate phosphatase 2 regulates pancreatic islet β-cell endoplasmic reticulum stress and proliferation. *The Journal of Biological Chemistry, 291*, 12029–12038.
43. Stoffel, W., LeKim, D., & Sticht, G. (1969). Distribution and properties of dihydrosphingosine-1-phosphate aldolase (sphinganine-1-phosphate alkanal-lyase). *Hoppe-Seyler's Zeitschrift für Physiologische Chemie, 350*, 1233–1241.
44. Bourquin, F., Riezman, H., Capitani, G., & Grutter, M. G. (2010). Structure and function of sphingosine-1-phosphate lyase, a key enzyme of sphingolipid metabolism. *Structure, 18*, 1054–1065.
45. Borowsky, A. D., Bandhuvula, P., Kumar, A., Yoshinaga, Y., Nefedov, M., Fong, L. G., Zhang, M., Baridon, B., Dillard, L., de Jong, P., Young, S. G., West, D. B., & Saba, J. D. (2012). Sphingosine-1-phosphate lyase expression in embryonic and adult murine tissues. *Journal of Lipid Research, 53*, 1920–1931.
46. Schwab, S. R., Pereira, J. P., Matloubian, M., Xu, Y., Huang, Y., & Cyster, J. G. (2005). Lymphocyte sequestration through S1P lyase inhibition and disruption of S1P gradients. *Science, 309*, 1735–1739.
47. Saba, J. D. (2019). Fifty years of lyase and a moment of truth: Sphingosine phosphate lyase from discovery to disease. *Journal of Lipid Research, 60*, 456–463.
48. Schmahl, J., Raymond, C. S., & Soriano, P. (2007). PDGF signaling specificity is mediated through multiple immediate early genes. *Nature Genetics, 39*, 52–60.
49. Weber, C., Krueger, A., Munk, A., Bode, C., Van Veldhoven, P. P., & Graler, M. H. (2009). Discontinued postnatal thymocyte development in sphingosine 1-phosphate-lyase-deficient mice. *Journal of Immunology, 183*, 4292–4301.
50. Vogel, P., Donoviel, M. S., Read, R., Hansen, G. M., Hazlewood, J., Anderson, S. J., Sun, W., Swaffield, J., & Oravecz, T. (2009). Incomplete inhibition of sphingosine 1-phosphate lyase modulates immune system function yet prevents early lethality and non-lymphoid lesions. *PLoS One, 4*, e4112.
51. Allende, M. L., Bektas, M., Lee, B. G., Bonifacino, E., Kang, J., Tuymetova, G., Chen, W., Saba, J. D., & Proia, R. L. (2011). Sphingosine-1-phosphate lyase deficiency produces a pro-inflammatory response while impairing neutrophil trafficking. *The Journal of Biological Chemistry, 286*, 7348–7358.
52. Bektas, M., Allende, M. L., Lee, B. G., Chen, W., Amar, M. J., Remaley, A. T., Saba, J. D., & Proia, R. L. (2010). Sphingosine 1-phosphate lyase deficiency disrupts lipid homeostasis in liver. *The Journal of Biological Chemistry, 285*, 10880–10889.
53. Hagen, N., Van Veldhoven, P. P., Proia, R. L., Park, H., Merrill, A. H., & van Echten-Deckert, G. (2009). Subcellular origin of sphingosine 1-phosphate is essential for its toxic effect in lyase-deficient neurons. *The Journal of Biological Chemistry, 284*, 11346–11353.
54. Degagne, E., Pandurangan, A., Bandhuvula, P., Kumar, A., Eltanawy, A., Zhang, M., Yoshinaga, Y., Nefedov, M., de Jong, P. J., Fong, L. G., Young, S. G., Bittman, R., Ahmedi, Y., & Saba, J. D. (2014). Sphingosine-1-phosphate lyase downregulation promotes colon carcinogenesis through STAT3-activated microRNAs. *The Journal of Clinical Investigation, 124*, 5368–5384.
55. Morgan, A. R., Turic, D., Jehu, L., Hamilton, G., Hollingworth, P., Moskvina, V., Jones, L., Lovestone, S., Brayne, C., Rubinsztein, D. C., Lawlor, B., Gill, M., O'Donovan, M. C., Owen, M. J., & Williams, J. (2007). Association studies of 23 positional/functional candidate genes on chromosome 10 in late-onset Alzheimer's disease. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics, 144B*, 762–770.

56. Hla, T., Venkataraman, K., & Michaud, J. (2008). The vascular S1P gradient-cellular sources and biological significance. *Biochimica et Biophysica Acta, 1781*, 477–482.
57. Fukuhara, S., Simmons, S., Kawamura, S., Inoue, A., Orba, Y., Tokudome, T., Sunden, Y., Arai, Y., Moriwaki, K., Ishida, J., Uemura, A., Kiyonari, H., Abe, T., Fukamizu, A., Hirashima, M., Sawa, H., Aoki, J., Ishii, M., & Mochizuki, N. (2012). The sphingosine-1-phosphate transporter Spns2 expressed on endothelial cells regulates lymphocyte trafficking in mice. *The Journal of Clinical Investigation, 122*, 1416–1426.
58. Hisano, Y., Kobayashi, N., Yamaguchi, A., & Nishi, T. (2012). Mouse SPNS2 functions as a sphingosine-1-phosphate transporter in vascular endothelial cells. *PLoS One, 7*, e38941.
59. Nijnik, A., Clare, S., Hale, C., Chen, J., Raisen, C., Mottram, L., Lucas, M., Estabel, J., Ryder, E., Adissu, H., Sanger Mouse Genetics Project, Adams, N. C., Ramirez-Solis, R., White, J. K., Steel, K. P., Dougan, G., & Hancock, R. E. (2012). The role of sphingosine-1-phosphate transporter Spns2 in immune system function. *Journal of Immunology, 189*, 102–111.
60. Mendoza, A., Breart, B., Ramos-Perez, W. D., Pitt, L. A., Gobert, M., Sunkara, M., Lafaille, J. J., Morris, A. J., & Schwab, S. R. (2012). The transporter Spns2 is required for secretion of lymph but not plasma sphingosine-1-phosphate. *Cell Reports, 2*, 1104–1110.
61. Mendoza, A., Fang, V., Chen, C., Serasinghe, M., Verma, A., Muller, J., Chaluvadi, V. S., Dustin, M. L., Hla, T., Elemento, O., Chipuk, J. E., & Schwab, S. R. (2017). Lymphatic endothelial S1P promotes mitochondrial function and survival in naive T cells. *Nature, 546*, 158–161.
62. Fang, V., Chaluvadi, V. S., Ramos-Perez, W. D., Mendoza, A., Baeyens, A., Rivera, R., Chun, J., Cammer, M., & Schwab, S. R. (2017). Gradients of the signaling lipid S1P in lymph nodes position natural killer cells and regulate their interferon-gamma response. *Nature Immunology, 18*, 15–25.
63. Wang, Z., Zheng, Y., Wang, F., Zhong, J., Zhao, T., Xie, Q., Zhu, T., Ma, F., Tang, Q., Zhou, B., & Zhu, J. (2020). Mfsd2a and Spns2 are essential for sphingosine-1-phosphate transport in the formation and maintenance of the blood-brain barrier. *Science Advances, 6*, eaay8627.
64. Vu, T. M., Ishizu, A. N., Foo, J. C., Toh, X. R., Zhang, F., Whee, D. M., Torta, F., Cazenave-Gassiot, A., Matsumura, T., Kim, S., Toh, S. E. S., Suda, T., Silver, D. L., Wenk, M. R., & Nguyen, L. N. (2017). Mfsd2b is essential for the sphingosine-1-phosphate export in erythrocytes and platelets. *Nature, 550*, 524–528.
65. Chandrakanthan, M., Nguyen, T. Q., Hasan, Z., Muralidharan, S., Vu, T. M., Li, A. W. L., Le, U. T. N., Ha, H. T. T., Baik, S.-H., Tan, S. H., Foo, J. C., Wenk, M. R., Cazenave-Gassiot, A., Torta, F., Ong, W. Y., Chan, M. Y. Y., & Nguyen, L. N. (2021). Deletion of Mfsd2b impairs thrombotic functions of platelets. *Nature Communications, 12*, 2286.
66. Okuniewska, M., Fang, V., Baeyens, A., Raghavan, V., Lee, J. Y., Littman, D. R., & Schwab, S. R. (2021). SPNS2 enables T cell egress from lymph nodes during an immune response. *Cell Reports, 36*, 109368.
67. Kawahara, A., Nishi, T., Hisano, Y., Fukui, H., Yamaguchi, A., & Mochizuki, N. (2009). The sphingolipid transporter spns2 functions in migration of zebrafish myocardial precursors. *Science, 323*, 524–527.
68. Kobayashi, N., Kawasaki-Nishi, S., Otsuka, M., Hisano, Y., Yamaguchi, A., & Nishi, T. (2018). MFSD2B is a sphingosine 1-phosphate transporter in erythroid cells. *Scientific Reports, 8*, 4969.
69. Cater, R. J., Chua, G. L., Erramilli, S. K., Keener, J. E., Choy, B. C., Tokarz, P., Chin, C. F., Quek, D. Q. Y., Kloss, B., Pepe, J. G., Parisi, G., Wong, B. H., Clarke, O. B., Marty, M. T., Kossiakoff, A. A., Khelashvili, G., Silver, D. L., & Mancia, F. (2021). Structural basis of omega-3 fatty acid transport across the blood-brain barrier. *Nature, 595*, 315–319.
70. Wood, C. A. P., Zhang, J., Aydin, D., Xu, Y., Andreone, B. J., Langen, U. H., Dror, R. O., Gu, C., & Feng, L. (2021). Structure and mechanism of blood-brain-barrier lipid transporter MFSD2A. *Nature, 596*, 444–448.
71. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Zidek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature, 596*, 583–589.
72. Murata, N., Sato, K., Kon, J., Tomura, H., Yanagita, M., Kuwabara, A., Ui, M., & Okajima, F. (2000). Interaction of sphingosine 1-phosphate with plasma components, including lipoproteins, regulates the lipid receptor-mediated actions. *The Biochemical Journal, 352*(Pt 3), 809–815.
73. Obinata, H., Kuo, A., Wada, Y., Swendeman, S., Liu, C. H., Blaho, V. A., Nagumo, R., Satoh, K., Izumi, T., & Hla, T. (2019). Identification of ApoA4 as a sphingosine 1-phosphate chaperone in ApoM- and albumin-deficient mice. *Journal of Lipid Research, 60*, 1912–1921.
74. Christoffersen, C., Obinata, H., Kumaraswamy, S. B., Galvani, S., Ahnstrom, J., Sevvana, M., Egerer-Sieber, C., Muller, Y. A., Hla, T., Nielsen, L. B., & Dahlback, B. (2011). Endothelium-protective sphingosine-1-phosphate provided by HDL-associated apolipoprotein M. *Proceedings of the National Academy of Sciences of the United States of America, 108*, 9613–9618.
75. Liu, M., Seo, J., Allegood, J., Bi, X., Zhu, X., Boudyguina, E., Gebre, A. K., Avni, D., Shah, D., Sorci-Thomas, M. G., Thomas, M. J., Shelness, G. S., Spiegel, S., & Parks, J. S. (2014). Hepatic apolipoprotein M (apoM) overexpression stimulates formation of larger apoM/sphingosine 1-phosphate-enriched plasma high density lipoprotein. *The Journal of Biological Chemistry, 289*, 2801–2814.

76. Ruiz, M., Okada, H., & Dahlback, B. (2017). HDL-associated ApoM is anti-apoptotic by delivering sphingosine 1-phosphate to S1P1 & S1P3 receptors on vascular endothelium. *Lipids in Health and Disease, 16*, 36.
77. Ruiz, M., Frej, C., Holmer, A., Guo, L. J., Tran, S., & Dahlback, B. (2017). High-density lipoprotein-associated Apolipoprotein M limits endothelial inflammation by delivering Sphingosine-1-Phosphate to the Sphingosine-1-Phosphate Receptor 1. *Arteriosclerosis, Thrombosis, and Vascular Biology, 37*, 118–129.
78. Swendeman, S. L., Xiong, Y., Cantalupo, A., Yuan, H., Burg, N., Hisano, Y., Cartier, A., Liu, C. H., Engelbrecht, E., Blaho, V., Zhang, Y., Yanagida, K., Galvani, S., Obinata, H., Salmon, J. E., Sanchez, T., Di Lorenzo, A., & Hla, T. (2017). An engineered S1P chaperone attenuates hypertension and ischemic injury. *Science Signaling, 10*(492), eaal2722.
79. Bode, C., Sensken, S. C., Peest, U., Beutel, G., Thol, F., Levkau, B., Li, Z., Bittman, R., Huang, T., Tolle, M., van der Giet, M., & Graler, M. H. (2010). Erythrocytes serve as a reservoir for cellular and extracellular sphingosine 1-phosphate. *Journal of Cellular Biochemistry, 109*, 1232–1243.
80. Kurano, M., & Yatomi, Y. (2018). Sphingosine 1-phosphate and atherosclerosis. *Journal of Atherosclerosis and Thrombosis, 25*, 16–26.
81. Chun, J., Hla, T., Lynch, K. R., Spiegel, S., & Moolenaar, W. H. (2010). International Union of Basic and Clinical Pharmacology. LXXVIII. Lysophospholipid receptor nomenclature. *Pharmacological Reviews, 62*, 579–587.
82. Foord, S. M., Bonner, T. I., Neubig, R. R., Rosser, E. M., Pin, J. P., Davenport, A. P., Spedding, M., & Harmar, A. J. (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacological Reviews, 57*, 279–288.
83. Blaho, V. A., & Hla, T. (2014). An update on the biology of sphingosine 1-phosphate receptors. *Journal of Lipid Research, 55*, 1596–1608.
84. Means, C. K., & Brown, J. H. (2009). Sphingosine-1-phosphate receptor signalling in the heart. *Cardiovascular Research, 82*, 193–200.
85. Li, C., Kong, Y., Wang, H., Wang, S., Yu, H., Liu, X., Yang, L., Jiang, X., Li, L., & Li, L. (2009). Homing of bone marrow mesenchymal stem cells mediated by sphingosine 1-phosphate contributes to liver fibrosis. *Journal of Hepatology, 50*, 1174–1183.
86. Kono, Y., Nishiuma, T., Nishimura, Y., Kotani, Y., Okada, T., Nakamura, S., & Yokoyama, M. (2007). Sphingosine kinase 1 regulates differentiation of human and mouse lung fibroblasts mediated by TGF-beta1. *American Journal of Respiratory Cell and Molecular Biology, 37*, 395–404.
87. Zhang, X., Ritter, J. K., & Li, N. (2018). Sphingosine-1-phosphate pathway in renal fibrosis. *American Journal of Physiology. Renal Physiology, 315*, F752–F756.
88. Engelbrecht, E., Levesque, M. V., He, L., Vanlandewijck, M., Nitzsche, A., Niazi, H., Kuo, A., Singh, S. A., Aikawa, M., Holton, K., Proia, R. L., Kono, M., Pu, W. T., Camerer, E., Betsholtz, C., & Hla, T. (2020). Sphingosine 1-phosphate-regulated transcriptomes in heterogenous arterial and lymphatic endothelium of the aorta. *eLife, 9*, e52690.
89. Ramos-Perez, W. D., Fang, V., Escalante-Alcalde, D., Cammer, M., & Schwab, S. R. (2015). A map of the distribution of sphingosine 1-phosphate in the spleen. *Nature Immunology, 16*, 1245–1252.
90. Hisano, Y., Kono, M., Cartier, A., Engelbrecht, E., Kano, K., Kawakami, K., Xiong, Y., Piao, W., Galvani, S., Yanagida, K., Kuo, A., Ono, Y., Ishida, S., Aoki, J., Proia, R. L., Bromberg, J. S., Inoue, A., & Hla, T. (2019). Lysolipid receptor cross-talk regulates lymphatic endothelial junctions in lymph nodes. *The Journal of Experimental Medicine, 216*, 1582–1598.
91. Shi, X., Wang, W., Li, J., Wang, T., Lin, Y., Huang, S., Kuver, A., Chen, C., Hla, T., Li, X., & Dai, K. (2019). Sphingosine 1-phosphate receptor 1 regulates cell-surface localization of membrane proteins in endothelial cells. *Biochimica et Biophysica Acta—General Subjects, 1863*, 1079–1087.
92. Wang, B., Dong, N., Wu, D., Fang, Y., Chen, J., Lin, Y., Bellusci, S., Zhang, J. S., Dai, K., & Chen, C. (2022). Sphingosine 1-phosphate receptor 1 governs endothelial barrier function and angiogenesis by upregulating endoglin signaling. *Annals of Translational Medicine, 10*(3), 136. https://doi.org/10.21037/atm-21-6679
93. Hanson, M. A., Roth, C. B., Jo, E., Griffith, M. T., Scott, F. L., Reinhart, G., Desale, H., Clemons, B., Cahalan, S. M., Schuerer, S. C., Sanna, M. G., Han, G. W., Kuhn, P., Rosen, H., & Stevens, R. C. (2012). Crystal structure of a lipid G protein-coupled receptor. *Science, 335*, 851–855.
94. Schulze, T., Golfier, S., Tabeling, C., Rabel, K., Graler, M. H., Witzenrath, M., & Lipp, M. (2011). Sphingosine-1-phospate receptor 4 (S1P(4)) deficiency profoundly affects dendritic cell function and TH17-cell differentiation in a murine model. *The FASEB Journal, 25*, 4024–4036.
95. Walzer, T., Chiossone, L., Chaix, J., Calver, A., Carozzo, C., Garrigue-Antar, L., Jacques, Y., Baratin, M., Tomasello, E., & Vivier, E. (2007). Natural killer cell trafficking in vivo requires a dedicated sphingosine 1-phosphate receptor. *Nature Immunology, 8*, 1337–1344.
96. Jaillard, C., Harrison, S., Stankoff, B., Aigrot, M. S., Calver, A. R., Duddy, G., Walsh, F. S., Pangalos, M. N., Arimura, N., Kaibuchi, K., Zalc, B., & Lubetzki, C. (2005). Edg8/S1P5: An oligodendroglial receptor with dual function on process retraction and cell survival. *The Journal of Neuroscience, 25*, 1459–1469.
97. Novgorodov, A. S., El-Alwani, M., Bielawski, J., Obeid, L. M., & Gudz, T. I. (2007). Activation of sphingosine-1-phosphate receptor S1P5 inhibits oligodendrocyte progenitor migration. *The FASEB Journal, 21*, 1503–1514.